



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-101A(7)

Phase II Trial Of The Addition Of Ipilimumab (MDX-010) To Isolated Limb Infusion (ILI) With Standard Melphalan And Dactinomycin In The Treatment Of Advanced Unresectable Melanoma Of The Extremity

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Charlotte E. Ariyan, MD, PhD	Surgery
Co-Principal Investigator(s)/Department:	Mary S. Brady, MD, FACS	Surgery
Investigator(s)/Department:	Jedd Wolchok, MD, PhD Paul Chapman, MD Michael Postow, MD Kathy Panageas, DrPH Gerald O'Neill Lloyd J. Old, MD Robert Lefkowitz, MD	Medicine Medicine Medicine Epidemiology and Biostatistics Pharmacy Sloan-Kettering Institute Radiology
Consenting Professional(s)/Department:	Charlotte E. Ariyan, MD, PhD Mary S. Brady, MD, FACS Jedd Wolchok, MD, PhD Michael Postow, MD	Surgery Surgery Medicine Medicine

Please Note : A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites
Manhattan
West Harrison

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-101A(7)

Table of Contents

1.0	PROTOCOL SUMMARY AND/OR SCHEMA	5
2.0	OBJECTIVES AND SCIENTIFIC AIMS	5
2.1.	Primary Objective	5
2.2.	Secondary Objectives	5
3.0	BACKGROUND AND RATIONALE	6
3.1.	Research Hypothesis	6
3.2.	Product Development Rationale	6
3.2.1.	CTLA-4 and T Cell Activation	6
3.3.	Summary of Results of Investigational Program	7
3.3.1.	Pharmacology of Ipilimumab	7
3.3.2.	Pre-Clinical Toxicology of Ipilimumab	8
3.3.3.	Human Pharmacokinetics of Ipilimumab	8
3.3.4.	Clinical Safety with Ipilimumab	9
3.3.5.	Immune-Related Adverse Events (IRAEs) with Ipilimumab	9
3.3.6.	Clinical Efficacy of Ipilimumab	11
3.4.	Overall Risk/Benefit Assessment	12
3.5.	Study Rationale	13
3.5.1.	Treatment Options for Patients with Melanoma	13
3.5.2.	Isolated Limb Infusion	13
4.0	OVERVIEW OF STUDY DESIGN/INTERVENTION	14
4.1	Design	14
4.2	Intervention	14
5.0	THERAPEUTIC/DIAGNOSTIC AGENTS	16
5.1.	Investigational Product: IPILIMUMAB	16
5.1.1.	Identification	17
5.1.2.	Packaging and Labeling	17
5.1.3.	Storage, Handling, and Dispensing	17
5.1.4.	Drug Ordering and Accountability	17
5.1.5.	Ipilimumab Accountability	18
5.1.6.	Ipilimumab Destruction	18
6.0	CRITERIA FOR SUBJECT ELIGIBILITY	19
6.1	Subject Inclusion Criteria	19
6.2	Subject Exclusion Criteria	20
1)	Any other malignancy that requires active treatment.	20

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-101A(7)

6.3. Prohibited and Restricted Therapies During the Study	21
6.3.1. Prohibited Therapies	21
6.3.2. Restricted Therapies	21
6.3.3. Precautions	21
7.0 RECRUITMENT PLAN	21
8.0 PRETREATMENT EVALUATION	22
9.0 TREATMENT/INTERVENTION PLAN	22
9.1. Ipilimumab	25
9.1.1. Dose Calculations	25
9.1.2. Storage, Preparation, and Administration	26
9.1.3. Preparation and Administration Guidelines	26
9.1.4. Dose Modifications	27
10.0 EVALUATION DURING TREATMENT/INTERVENTION	28
10.1. Procedures by Visit	28
10.2. Study Completion or Early Discontinuation Visit	28
10.3. Study Drug Discontinuation	29
10.4. Study Materials	29
11.0 TOXICITIES/SIDE EFFECTS	29
11.1. Safety Assessments	29
11.2. Safety Evaluation	29
11.2.1. Safety with Ipilimumab	29
11.2.2. Safety related to ILI	30
11.3. Immune-Related Adverse Events (IRAEs): Definition, Monitoring, and Treatment	31
11.3.1. Treatment of Infusion Reactions Associated with Ipilimumab	32
11.3.2. Treatment of Ipilimumab-Related Isolated Drug Fever	33
12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT	33
12.1. Efficacy Evaluation	33
12.2. Definition of Measurable/Non-Measurable and Index/Non-Index Lesions	33
12.3. Definition of Measurable and Non-Measurable Lesions	33
12.4. Definition of Index/Non-Index Lesions	34
12.5. Definition of Tumor Response Using irRC	34
12.6. Definition of Index Lesions Response Using irRC	34
12.7. Definition of Non-Index Lesions Response Using irRC	35
12.8. Impact of New Lesions on irRC	35
12.9. Definition of Overall Response Using irRC	35



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-101A(7)

12.10.	Immune-Related Best Overall Response Using irRC (irBOR)	36
12.11.	Response Endpoints	36
13.0	CRITERIA FOR REMOVAL FROM STUDY	37
13.1.	Discontinuation of Study Therapy	37
13.2.	Permanent Discontinuation for Related Adverse Events	37
13.3.	Exceptions to Permanent Discontinuation	38
14.0	BIostatISTICS	38
15.0	RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES	39
15.1	Research Participant Registration	39
15.2	Randomization	39
	This study does not involve randomization	39
16.0	DATA MANAGEMENT ISSUES	39
16.1	Quality Assurance	39
16.1.1.	Compliance with the Protocol and Protocol Revisions	39
16.1.2.	Informed Consent	40
16.1.3.	Records and Reports	40
16.1.4.	Good Clinical Practice	40
16.1.5.	Institutional Review Board/Independent Ethics Committee (IRB/IEC)	41
16.1.6.	Records Retention	41
16.2	Data and Safety Monitoring	41
17.0	PROTECTION OF HUMAN SUBJECTS	42
17.1	Privacy	42
17.2	Serious Adverse Event (SAE) Reporting	42
17.2.1		43
18.0	INFORMED CONSENT PROCEDURES	48
19.0	REFERENCES	49
20.0	APPENDICES	50



1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Research Hypothesis:	The addition of systemic Ipilimumab to regional therapy in patients with Stage IIIB, IIIC or Stage IV Melanoma will improve progression free survival. The hypothesis is that the cell death occurring with regional chemotherapy can be a priming event for the immune system. Systemic administration of Ipilimumab may then augment the immune response and may delay disease progression.
Study Schema: Drugs / Doses / Length of Treatment)	Patients with Stage IIIB, IIIC or IV melanoma eligible for an isolated limb infusion (ILI), will be considered for the trial in which they will receive additional systemic treatment with Ipilimumab. Induction therapy with Ipilimumab will start 1-3 weeks after ILI in the standard dose of 10mg/kg every 3 weeks for a total of 4 doses. Patients will then receive chronic therapy every 3 months. Patients will be followed every 3 months for 2 years, with PFS measured by CT Scan and physical exam at one year.
Study Objectives: Primary: Secondary:	The primary objective is to determine progression free survival (PFS), over historical controls at one year. The secondary objectives are: 1) To determine the safety of additional Ipilimumab. 2) To determine response rates and evaluate the distribution of PFS (within the affected limb or systemically) with combination therapy. 3) To define the immunologic events and signatures at the tumor site and in the periphery that correspond to response to Ipilimumab.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1. Primary Objective

The primary objective is to determine progression free survival at one year.

2.2. Secondary Objectives

The secondary objectives are:

- 1) To determine the safety of additional Ipilimumab.
- 2) To determine response rates of combination therapy.
- 3) To define the immunologic events and signatures at the tumor site and in the periphery that corresponds to response to Ipilimumab.

This protocol will investigate the effect of the addition of immunotherapy with Ipilimumab (MDX-010) to standard regional chemotherapy in the setting of advanced extremity melanoma (Stage IIIB, IIIC

or Stage IV melanoma). Patients eligible to undergo an isolated limb infusion (ILI) will be offered additional systemic treatment with Ipilimumab. Patients will be treated with systemic Ipilimumab *after* ILI in the standard dose of 10 mg/kg every 3 weeks for a total of 4 doses, followed by maintenance therapy every 3 months (+/- 2 weeks) for 2 years. Patients will be on-study for 2 years. The primary objective is to study the safety and efficacy in this patient population with the primary efficacy measure defined as progression-free survival at 1 year (48-54 weeks).

3.0 BACKGROUND AND RATIONALE

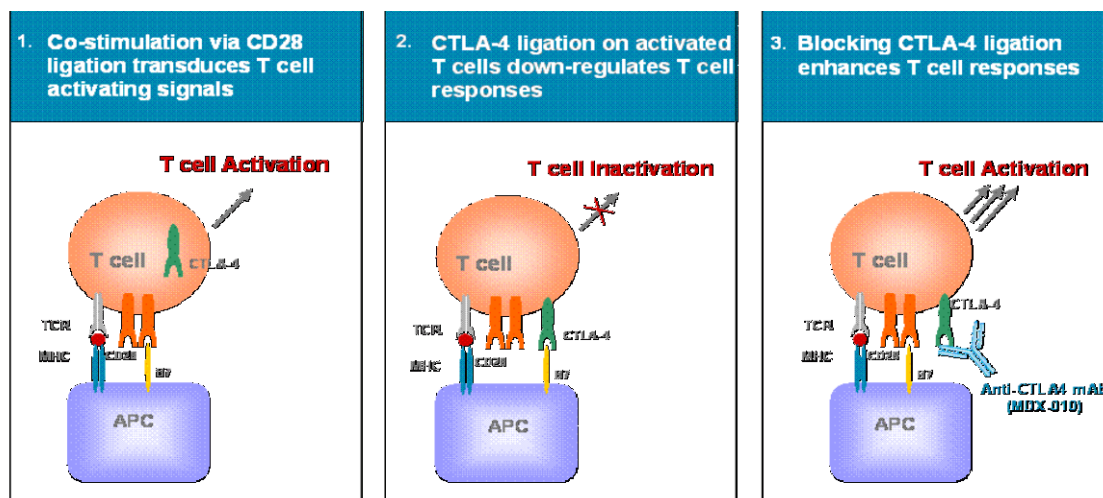
3.1. Research Hypothesis

The addition of systemic Ipilimumab to regional therapy in patients with Stage IIIB, IIIC, or Stage IV melanoma will improve progression free survival. The hypothesis is that the cell death occurring with regional chemotherapy can be a priming event for the immune system. Systemic administration of Ipilimumab may then augment this immune response, and delay melanoma progression.

3.2. Product Development Rationale

3.2.1. CTLA-4 and T Cell Activation

Figure 1 Mechanism of Action



Advances in the understanding of the mechanisms that regulate T cell activation have allowed the rational design of new strategies for immunotherapy of tumors, including melanoma. It has been known for some time that engagement of the T cell antigen receptor by itself is not sufficient for full T cell activation; a second co-stimulatory signal is required for induction of IL-2 production, proliferation and differentiation to effector function of naive T cells. Abundant data now indicate that the primary source of this costimulation is mediated by engagement of CD28 on the T cell surface by members of the B7 family on the antigen-presenting cell (APC)[1].(See Figure 1.)

Expression of B7 has been shown to be limited to “professional” antigen presenting cells; that is, specialized cells of the hematopoietic lineage, including dendritic cells, activated macrophages, and activated B cells. It has been suggested that this sharply-defined restriction of B7 expression is a fail-safe mechanism for maintenance of peripheral T cell tolerance, insuring that T cell activation can

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

only be stimulated by appropriate APCs.[2] The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses.[3, 4]

The demonstration that induction of expression of B7 on many tumor cells by transfection, transduction, or other mechanisms can heighten tumor immunogenicity led to great interest in pursuing this as an approach to tumor immunotherapy. As demonstrated in vivo in murine tumor models, the utility of B7 expression as a vaccination approach is limited by the following factors: (1) B7-expressing tumor cell vaccines are only effective when the tumor cells have a high degree of inherent immunogenicity; (2) while B7-expressing vaccines have been shown in many cases to be effective in inducing protective immune responses, they have demonstrated only limited utility in inducing responses to established tumors; and (3) inactivation of tumor cells by radiation has been shown to destroy the immuno-enhancing activity of the B7 gene product.[5, 6]

In the past few years it has become apparent that co-stimulation is even more complex than originally thought. After activation, T cells express CTLA-4, a close homologue to CD28. CTLA-4 binds members of the B7 family with a much higher affinity than CD28[7]. Although there was initially some controversy as to the role of CTLA-4 in regulating T cell activation, it has become clear that CTLA-4 down-regulates T cell responses[8]. This was initially suggested by the following in vitro observations: (1) blockade of CTLA-4/B7 interactions with antibody enhanced T cell responses; (2) cross-linking of CTLA-4 with CD3 and CD28 inhibited T cell responses; and (3) administration of antibodies to CTLA-4 in vivo enhanced the immune response to peptide antigens or superantigens in mice.[9-12] Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro[10]

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation[13-15]. CTLA-4 knockout mice appear to have spontaneously activated T cells evident at approximately 1 week after birth, followed by rampant lymphoproliferation and lymphadenopathy. These mice die at approximately 3 weeks of age, either as a result of polyclonal T cell expansion and tissue destruction or as a result of toxic shock resulting from lymphokine production by the T cells. Since thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice, the rampant T cell expansion that occurs in the mice indicates that CTLA-4 plays a critical role in down-regulating T cell responses in the periphery[7].

3.3. Summary of Results of Investigational Program

3.3.1. Pharmacology of Ipilimumab

Ipilimumab is a human immunoglobulin G (IgG1) κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys.

Ipilimumab was originally produced and purified from a hybridoma clone. Subsequently, a transfectoma (CHO cell) has been generated that is capable of producing more ipilimumab on a per cell basis than the hybridoma. Material from the transfectoma will be utilized in this and future

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

ipilimumab clinical studies. Biochemical, immunologic and in vivo preclinical primate assessments demonstrated similarity between hybridoma and transfectoma-derived ipilimumab.

3.3.2. Pre-Clinical Toxicology of Ipilimumab

Complete information on the pre-clinical toxicology studies can be found in the Ipilimumab Investigator Brochure (IB). Non-clinical toxicity assessments included in vitro evaluation for the potential of ipilimumab to mediate complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC), and toxicology assessments in cynomolgus monkeys alone and in the presence of vaccines.

The in vitro studies demonstrated that ipilimumab did not mediate CDCC of PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 ug/mL. These data are consistent with the requirement of high levels of antigen expression on the surface of target cells for efficient ADCC or CDCC. Since ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that ipilimumab treatment would not result in depletion of activated T cells in- vivo. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

No mortality or signs of toxicity were observed in three independent 14-day intravenous toxicology studies in cynomolgus monkeys at multiple doses up to 30 mg/kg/dose. Furthermore, ipilimumab was evaluated in sub chronic and chronic toxicology studies in cynomolgus monkeys with and without Hepatitis B (HepB) Vaccine and Melanoma Vaccine. Ipilimumab was well tolerated alone or in combination in all studies. There were no significant changes in clinical signs, body weight values, clinical pathology values or T cell activation markers. In addition, there were no significant histopathology changes in the stomach or colon.

3.3.3. Human Pharmacokinetics of Ipilimumab

Pharmacokinetic (PK) profiles for ipilimumab have been analyzed. The primary objective of Protocol MDX010-015 was to determine the safety and PK profile of single and multiple doses of ipilimumab derived from a transfectoma or hybridoma cell line. Mean plasma concentrations of ipilimumab administered at doses of 3 mg/kg (hybridoma-derived drug product); 2.8 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, and 20 mg/kg (transfectoma-derived drug product) demonstrated approximate dose proportionality. Equimolar doses of hybridoma-derived and transfectoma-derived drug product had comparable PK profiles. The range of mean volume of distribution at steady state (Vss) across cohorts 2.8, 3, 5, 7.5, 10, 15, and 20 mg/kg, was 57.3 to 82.6 mL/kg, indicating drug distribution was mostly limited to the intravascular space. The clearance was low (range 0.11 to 0.29 mL/h/kg) and reflective of the half-life (range 297 to 414 h), which is consistent with the long terminal disposition phase of ipilimumab. There was moderate variability in the PK parameters among subjects, with CV of 11% to 48% in AUC(0-21d), 20% to 59% in CL, and 17% to 46% in Vss.



3.3.4. Clinical Safety with Ipilimumab

Ipilimumab immunotherapy is currently under investigation in patients with unresectable advanced melanoma (unresectable Stage III or Stage IV) to potentially demonstrate an improvement on a large unmet medical need in this population.

Ipilimumab has been administered to approximately 2633 patients with different cancers in 24 completed or ongoing clinical trials as of 31-Mar-2008 with a dose range between 0.3 mg/kg and 20 mg/kg. Most experience with ipilimumab exists at the 3 mg/kg and 10 mg/kg dose levels. Patients who received ipilimumab at 3 mg/kg were treated in clinical studies conducted early in the development program and received either a single or multiple injections. Intra-patient dose escalation indicated that patients who were unresponsive at the 3 mg/kg dose level may have responded to 9 mg/kg. Based on preliminary data on the 10 mg/kg dose level of ipilimumab, the ongoing clinical program investigating ipilimumab in metastatic melanoma utilizes the 10 mg/kg dose level with the expectation that 10 mg/kg will prove more beneficial than 3 mg/kg. Most recently, treatment with ipilimumab was demonstrated to improve survival at 3mg/kg in patients with Stage IV melanoma[16].

3.3.4.1. Details of Drug-Related Adverse Events

Drug-related adverse events (AEs) were reported in studies with ipilimumab as monotherapy as well as in combination studies with vaccines, cytokines or chemotherapy. The AE profile of ipilimumab is relatively well characterized, with most drug-related AEs being immune-related adverse events (IRAEs), which are considered to be associated with the mechanism of action of ipilimumab. The most common IRAEs are colitis and diarrhea, rash, pruritis, deficiencies of endocrine organs (pituitary, adrenal or thyroid), hepatitis, and uveitis. Rare complications are bowel perforations (~1%) resulting from underlying severe colitis, which have required surgical intervention.

3.3.4.2. Drug-Related Serious Adverse Events

Drug-related Grade 3 or Grade 4 serious adverse events (SAEs) include: rash/desquamation, pruritus, uveitis, speech impairment, abdominal pain, diarrhea/colitis, nausea/vomiting, transaminase elevation, adrenal insufficiency, panhypopituitarism and atrial fibrillation. Some of these events, such as rash/desquamation, pruritus, uveitis, diarrhea/colitis, transaminase elevation, adrenal insufficiency and panhypopituitarism, may represent drug induced IRAEs (see Section 4.3.4). Refer to the most recent version of the Ipilimumab Investigator Brochure for the latest update on SAEs.

Among subjects treated with ipilimumab 10 mg/kg, SAEs considered possibly, probably, or definitely related to study drug were reported for 26% of subjects (176/675). Drug related SAEs reported in at least 1% of the 675 subjects at 10 mg/kg included diarrhea (10%), colitis (7%), vomiting (3%), dehydration (3%), autoimmune hepatitis (2%), hypopituitarism (2%), nausea (2%), abdominal pain (2%), pyrexia (2%), aspartate aminotransferase increased (1%), alanine aminotransferase increased (1%), and fatigue (1%).

3.3.5. Immune-Related Adverse Events (IRAEs) with Ipilimumab

Many of the adverse events considered related to ipilimumab may be immune in nature and presumably a consequence of the intrinsic biological activity of ipilimumab. An IRAE is defined as



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

any adverse event associated with drug exposure and consistent with an immune-mediated event. Disease progression, infections and other etiologic causes are ruled out or deemed unlikely as contributing to the event. Supportive data, such as autoimmune serology tests or biopsies, are helpful but not necessary to deem an event an IRAE. Events of unclear etiology which were plausibly “immune-mediated” have been conservatively categorized as IRAEs even if serologic or histopathology data are absent. These IRAEs likely reflect a loss of tolerance to some self antigens or an unchecked immune response to gut or skin flora. Some breakthrough of immunity may be inseparably linked to the clinical antitumor activity of ipilimumab.

Approximately 60% of subjects developed any grade IRAEs which involved predominately the gastrointestinal (GI) tract, endocrine glands, liver, or skin. Based on data from the safety database, the number of subjects with serious IRAEs was approximately 15% (401/2633), including 8.2% for serious GI IRAEs (diarrhea and/or colitis), 2.2% of serious endocrinopathy (primarily hypophysitis/hypopituitarism) and <1% of serious skin IRAEs. Bowel perforation was reported in approximately 1% of subjects. With few exceptions these IRAEs were clinically manageable and reversible with supportive care or corticosteroids. In responding patients, addition of corticosteroids does not appear to have a temporal relationship to change in objective tumor response.

Additionally, as of February 2006, there has been observation from a National Cancer Institute (NCI) study of bowel wall perforation in some patients who were administered a high-dose IL-2 following treatment with ipilimumab. Of the 22 patients administered high-dose IL-2, three patients experienced bowel wall perforations. This is a higher rate than would be expected with high-dose IL-2 treatment alone. All three patients had metastatic melanoma and had previously received their last dose of ipilimumab > 77 days before the first dose of IL-2. Two of the patients had clinically significant ipilimumab-related diarrhea or colitis and the symptoms had completely resolved prior to IL-2 administration. One patient did not experience ipilimumab-related diarrhea. It is unknown whether this observation represents a true association or is mechanistically unrelated to prior ipilimumab exposure.

3.3.5.1. Drug-Related Deaths

Based on reports from the safety data base as of June 30, 2008, there have been reports of death (approximately 1% [28/3000]), deemed by the investigator as possibly related to the administration of study drug. The most common cause of drug related deaths was GI perforation. Other causes included multiorgan failure, sepsis, hypotension, acidosis, and adult respiratory distress syndrome. For details on all drug-related deaths, refer to the current version of the Ipilimumab Investigator Brochure.

3.3.5.2. Safety of 10 mg/kg Multiple Doses

Based on a review of the program-wide SAE data as previously reported, evidence had suggested that ipilimumab-associated irAEs were dose dependent in frequency, and higher irAE rates had been observed at 10 mg/kg than at lower doses of ipilimumab. Subsequently, this dose-dependent effect was further demonstrated in CA184-022 in which three dose levels of ipilimumab were studied, including 0.3 vs 3 vs 10 mg/kg. Table 1 summarizes the overall irAE frequencies by dose from CA184-022 based on safety data from the locked clinical database.



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-101A(7)

Qualitatively, the safety profile of ipilimumab at 10 mg/kg remains consistent with the low-dose safety profile in that most of the drug-related SAEs are characteristic of immune-related toxicity, and most of the irAEs are reported in the GI, hepatic, and endocrine systems. However, the data presented in Table 1 suggest that the frequency of irAEs in association with 10 mg/kg of ipilimumab at multiple doses is higher compared with the irAE frequency reported for lower doses.

Table 1. Summary of Immune-Related AEs by Treatment Groups - Treated Subjects (CA184-022)

	Number of Subjects (%)		
	Ipilimumab		
	0.3 mg/kg (N=72)	3 mg/kg (N=71)	10 mg/kg (N=71)
Overall irAEs	26.4	64.8	70.4
Grade 3-4	0	7.0	25.4
GI irAEs	16.7	32.4	39.4
Grade 3-4	0	2.8	15.5
Hepatic irAEs	0	0	2.8
Grade 3-4	0	0	2.8
Endocrine irAEs	0	5.6	4.2
Grade 3-4	0	2.8	1.4
Skin irAEs	12.5	45.1	46.5
Grade 3-4	0	1.4	4.2

3.3.5.3. Neuropathies

Isolated cases of motor neuropathy of an autoimmune origin have been reported among patients treated with ipilimumab. Two cases have been diagnosed as Guillain-Barre syndrome (GBS), only one of which was considered study related. As of July 2, 2008, 15 cases of neuropathy SAEs have been reported. Of these, 13 were assessed as unrelated to study therapy because alternative etiologies, including brain metastases, spinal cord compression, or arterial thrombosis, were identified in almost every case.

3.3.6. Clinical Efficacy of Ipilimumab

Treatment with ipilimumab has demonstrated clinically important and durable tumor responses in several malignancies including melanoma, prostate cancer, and renal cell carcinoma. The most extensively studied tumor type has been malignant melanoma. Based on preliminary results, ipilimumab is active in patients with advanced stage malignant melanoma. The objective responses observed with ipilimumab may be considered durable as they have occurred across a spectrum of doses and schedules.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

Based on a preliminary analysis for study MDX010-15 involving ipilimumab 10 mg/kg multiple doses, 34.8% of patients (N = 23) were progression-free at 6 months and about 17.4% were progression-free at 1 year. In comparison, for Study MDX010-08 involving ipilimumab 3 mg/kg multiple doses, 10.8% patients (N = 37) had progression-free survival at 6 months and 8.4% at 1 year. Ipilimumab has also been studied in combination with chemotherapy (dacarbazine), melanoma vaccines (gp100), and cytokines (IL-2). Further details on clinical results can be found in the current version of the Ipilimumab Investigator Brochure.

3.3.6.1. Relationship Between Response and Immune Related Adverse Events in Patients with Metastatic Melanoma

Drug-related AEs of any grade considered to be immune-mediated in nature (irAEs) were reported for 54.0% of subjects in clinical studies of ipilimumab. These irAEs are a consequence of inhibiting CTLA-4 function and most were reported as Grade 1 or 2. An association between BORR and higher grade (Grade 3-4) irAEs was suggested in early studies of ipilimumab 3 mg/kg but this association was not observed in 4 Phase 2 studies of ipilimumab (CA184022, CA184008, CA184007 and CA184004). There were proportionally more subjects with irAEs of any grade who experienced response or stable disease than subjects without irAEs who experienced response or stable disease, but due to the small sample sizes, these observations were statistically inconclusive[17-19].

3.4. Overall Risk/Benefit Assessment

Results from the 3 primary efficacy studies of ipilimumab suggest that the 10 mg/kg dose is active and offers the best benefit to risk ratio based on a 27.1% to 35.1% rate of disease control and a favorable 1-year survival rate of 48.6% to 59.1% compared with that reported in the literature (25.5% to 35%)[20-23]. Substantial reductions in total tumor burden, including widely disseminated disease in the skin, lung, and/or other visceral disease sites, were reported. More than half the responses were reported in subjects staged with M1b or M1c advanced melanoma disease, which is most resistant to approved therapies. The kinetics of ipilimumab resulted in known patterns of clinical activity (CR, PR and SD) as well as novel patterns, characterized by reductions in total tumor burden, including existing and new lesions, after initial tumor volume increase and/or after appearance of new lesions. In the pretreated population at 10 mg/kg in 2 of the 3 studies, disease control after initial tumor volume increase and/or new lesions was reported for 9.7% of subjects. Across all 3 studies, stable disease was often accompanied by clinically relevant reductions in tumor burden compared to baseline. All patterns of response, including SD, appeared to result in favorable survival, based on 1-year survival rates.

Characteristic organ-specific inflammatory irAEs were reported with ipilimumab therapy, typically during induction therapy. IrAEs were mostly reversible within days to weeks following cessation of therapy or treatment with symptomatic therapy, corticosteroids or other anti-inflammatory agents, depending upon severity. Accumulated clinical experience resulted in detailed toxicity management guidelines (also termed algorithms), by use of which irAEs can be effectively managed, especially when irAEs are recognized early and subjects are treated in a timely fashion. This can minimize the occurrence of irAE complications, such as GI perforation/colectomy or hepatic failure.

Treatment with ipilimumab resulted in clinical activity in pretreated and previously untreated subjects with advanced melanoma. Clinically relevant reductions in the tumor burden from baseline were

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

reported, together with a preliminary evidence of improved overall survival compared with published survival rates. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-related toxicities, suggest an acceptable benefit to risk ratio.

3.5. Study Rationale

3.5.1. Treatment Options for Patients with Melanoma

Up to ten percent of patients with melanoma will develop local-regional recurrence, defined as in transit lesions or satellitosis, in the extremity after treatment[24]. Administration of systemic chemotherapy has poor results, yet local control with surgical amputation has resulted in a 30% five-year survival[25]. Because a substantial percentage of patients can be salvaged by aggressive treatment, strategies to refine the approach to local-regional recurrence have evolved over the years, and include regional chemotherapy.

3.5.2. Isolated Limb Infusion

Isolated limb infusion is a technique used to deliver high doses of chemotherapy agents locally. Since systemic absorption is minimal, and doses of chemotherapy 15-25 x the systemic dose can be used[26]. Most often, Melphalan is used alone or in combination with other agents. Technically this occurs by exclusion of the limb with a tourniquet, percutaneous vascular isolation of the inflow and outflow, and infusion of chemotherapeutic agents. Isolated limb infusion (ILI) was developed at the Sydney Melanoma Unit, which also has the world's largest experience. In a recent report, the overall response to the therapy was 84%, (38% of patients having a complete response, and 46% having a partial response), with a median survival of 38 months[27].²⁶ The response rate is highly variable across studies. This is in part secondary to the differences in which response is measured. In the Australian studies, a response is measured by the WHO criteria with 2 observations no less than 4 weeks apart. At MSKCC, we have measured response at a set time point at week 13-15. This is to allow the edema of the extremity to abate and therefore not record an early response that either 1) do not last for at least 3 months, or 2) is inflated by the lack of ability to accurately measure a swollen extremity. In the only prospective study, with careful follow-up by Dr. Brady and colleagues at MSKCC, ILI with Melphalan and Dactinomycin resulted in a 50% response rate with 23% of patients having a complete response(CR). The median duration of the CR was 12 months[28]. Biopsies of some responding lesions demonstrated pigment laden macrophages, suggesting that the ILI may involve the immune system. The toxicity of this regime was acceptable and no patients required an amputation.

The results of these studies demonstrate that limb infusion is a well tolerated procedure. Yet this approach remains palliative as most patients will have distant recurrence[29, 30]. Even in the Australian studies with high initial response rates, the median survival of Stage IV patients is only 16 months[30]. Prior studies with Ipilimumab and systemic chemotherapy with dacarbazine, have demonstrated safety and potentially an augmented clinical responses[31]. Therefore, one approach to maximize the results in regional disease would be to combine local chemotherapy with ILI with a



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

systemic therapy, such as Ipilimumab. The overall risk-benefit ratio for patients entering this protocol is therefore at least comparable to and possibly better than alternative options.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

- 1) To determine the progression free survival with the addition of Immunotherapy with Ipilimumab to standard limb infusion chemotherapy of Melphalan and Dactinomycin.
- 2) To determine the response rate, distribution of PFS, and safety of the addition of Ipilimumab.
- 3) To define the correlative immunologic events and signatures that correspond to response to Ipilimumab

Patients with Stage IIIB, IIIC or IV melanoma eligible for an isolated limb infusion (ILI), will be considered for the trial in which they will receive additional systemic treatment with Ipilimumab. Induction therapy with Ipilimumab will start 1-3 weeks after ILI in the standard dose of 10mg/kg every 3 weeks for a total of 4 doses. Patients will then receive chronic therapy every 3 months (+/- 2 weeks). Patients who have discontinued the study drug and have not progressed will be seen at all specified time points for the intended duration of the trial (+/- 4 weeks). Patients will be followed every 3 months for 2 years, with PFS measured by CT Scan and physical exam at one year.

4.2 Intervention

This is a single-institution phase II trial with a primary outcome of progression free survival (PFS). Patients with advanced Stage IIIB, Stage IIIC, or Stage IV melanoma requiring ILI will be candidates for the trial. These patients will be identified by the attending physician and offered participation. Prior to ILI, patients will undergo an extent of disease evaluation consisting of a CT scan or MRI of the brain, and a CT scan of the chest, abdomen and pelvis. The extremity lesions will be measured and photographed by medical photography. In the case of diffuse, numerous extremity lesions, three index lesions will be chosen to measure and characterize. In patients with deep lesions which are difficult to quantitate, a CT Scan or MRI of the extremity will also be performed. The patient will then undergo an ILI in the operating room under anesthesia as previously described and currently performed at MSKCC[28].

Melphalan and dactinomycin are added to 400 mL of heparinized normal saline for the lower extremity and 200 mL of heparinized normal saline for the upper extremity. The dose of Melphalan will be calculated by limb volume (7.5 – 10mg/L) corrected for ideal body weight, and not limited by anatomic site. The dose of Dactinomycin to be used is 75 mcg/L limb volume (maximum 500 mcg).

Calculating the Melphalan Dose

The dosage of melphalan should be corrected for ideal body weight by using the formula described below.

Melphalan dose per liter of limb volume to be infused (mg/L) × Calculated Volume of

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

extremity(L) × Ideal body weight(kg) ÷ Actual body weight(kg) = Corrected Melphalan Dose.

EXAMPLE for a leg with a calculated volume of 7 liters: 7.5mg/L × 7 liters × 80 ÷ 100 = 42 mg

Estimated Ideal Body Weight (kg) will be calculated as follows:

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.

Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

Melphalan-Dactinomycin Infusion

For the lower extremity, melphalan should be admixed with 400 mL of normal saline containing 1 unit/mL heparin, and for the upper extremity, melphalan should be admixed with 200 mL of normal saline containing 1 unit/mL heparin. *The bag should be spiked with a secondary set.*

Blood samples will be taken for research from each patient at the following time points: at ILI (pre-treatment), during induction phase of Ipilimumab (week 1-3, week 4-6, week 7-9, week 10-12, week 13-15), and at each infusion of Ipilimumab during the maintenance phase. If a patient is no longer receiving Ipilimumab while still on study, the patient will not have research bloods drawn. Tissue samples will be taken from each patient at the following time points throughout the study: during ILI, week 1-3 (optional, patient can refuse), and week 13-15 unless there is no lesion or pigmented scar to identify previous target lesion. An additional biopsy may be performed during the induction phase (prior to week 13-15), if the physician feels the patient is responding and the lesion is likely to be gone by week 13-15.

After recovery from ILI patients will be seen in the office to start therapy with Ipilimumab, 1-3 weeks after the ILI procedure. The variable time of dosing is to allow patients to recover from the toxicity of limb infusion. Patients who have resolution of toxicity to Wiederbink I-III will then receive Ipilimumab every 3 weeks (+/- a week) for a total of 4 total doses. Within, three weeks following the final dose of Ipilimumab the lesion site will be biopsied, unless there is no identifiable lesion or pigmented scar, and blood samples will again be taken for analysis. Patients will be allowed to skip a dose of Ipilimumab if the performance status is not adequate, but the dosing cannot be delayed (see Appendix 8 for study schema). This is, in part, secondary to the fact that Ipilimumab has a long half life, and it has been noted in the other previous trials that the safest approach is to skip a dose if there is any question of the patient's ability to tolerate the dose. Patients with severe swelling of an extremity may defer the biopsy after ILI (before Ipilimumab). In this case, a biopsy pre-treatment and after Ipilimumab will be the only biopsies the patient may have. In the case of a complete response by the week 13-15 evaluation time point, where there is no identifiable lesion or pigmented scar, a biopsy will not be performed. Patients that appear to be progressing on the 4 cycles of Ipilimumab will be re-imaged with a CT Scan to accurately evaluate for progression of disease (POD). Any demonstration of POD at that time point will allow for discontinuation of drug and switch to another therapy for metastatic melanoma. Patients who have not progressed will begin maintenance therapy with Ipilimumab. They will receive Ipilimumab every 3 months (+/- 2 weeks) for 2 years and will have research blood drawn at each dose of Ipilimumab during the maintenance therapy phase (months 6, 9, 12, 15, 18, 21, 24). Patients who have discontinued the study drug and have not progressed will be seen at all specified time points for the intended duration of the trial.

Amended: 09/16/15



The Wiederbink criteria will be used to assess toxicity, as shown in Appendix 7. A partial and complete response of the extremity will be assessed by using the extremity tumor measurement forms (see appendix 10) together with the immune-related response criteria (irRC) that incorporates the contribution of new measurable lesions.

During the maintenance phase CT Scans will be performed every 3 months (+/- 2 weeks). This will include a scan at 1 year (48-54 weeks) to assess for PFS.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1. Investigational Product: IPILIMUMAB

The investigational product is defined as a pharmaceutical form of an active ingredient being tested as a reference in the study, whether blinded or unblinded. In this study, the investigational product is ipilimumab. It should be noted that ipilimumab was FDA approved for patients with metastatic melanoma in March of 2011.

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products. In this protocol, noninvestigational product(s) is/are: Melphalan and Dactinomycin, as well as 5-HT anti-emetics.

Melphalan has been used for regional chemotherapy for metastatic melanoma since 1957 and is of proven efficacy and safety[19]. Melphalan is a phenylalanine derivative of nitrogen mustard and acts as an alkylating agent. It is actively transported in cells that actively take up phenylalanine or tyrosine such as melanoma. Melphalan uptake by the cell results in impaired transcription and single and double strand DNA breaks.

Melphalan is manufactured by Galazo Wellcome Co. The agent used in this trial will be stored in and maintained in the pharmacy at MSKCC. The intact package will be stored at room temperature and protected from light. Melphalan is supplied as a sterile diluent in a 10 ml volume. Each vial contains 6 ml of propylene glycol, 0.2 gm of sodium citrate and 0.5 ml of 95% ethanol. After reconstitution of the melphalan with the solvent the final concentration is 5mg/ml. The stock solution is diluted with sterile 0.9% NaCl to a concentration no greater than 2mg/ml prior to administration.

Reconstitution of Melphalan results in a solution that undergoes hydrolysis at room temperature. Reconstituted Melphalan retains 90% potency for approximately 3 hours at 30°C. Melphalan used in this investigation will be reconstituted within 20 minutes of administration.

The most common toxicity of systemic melphalan is myelosuppression, usually occurring with a nadir of 14-21 days, however, this effect is seen with systemic administration and has not occurred in patients undergoing ILI.

Dactinomycin is an antitumor antibiotic produced by streptomyces species in culture. The compound binds to DNA and inhibits DNA-dependent RNA synthesis. It is also a topoisomerase II



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

inhibitor. The major toxicity of dactinomycin is myelosuppression, usually beginning after the first week after treatment and reaching a nadir at 21 days. Nausea and vomiting occur with systemic administration, usually resolving within hours. Both agents will be prepared by the operating room pharmacy just prior to the procedure.

5.1.1. Identification

Ipilimumab is available in 5 mg/mL single-use vials (10 mL or 40 mL). The sterile solution in the vial is clear and colorless. Ipilimumab is administered via intravenous infusion only.

5.1.2. Packaging and Labeling

BMS will provide ipilimumab at no cost for this study. Ipilimumab will be provided in open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions, and dispensing instructions along with the Investigational New Drug (IND) caution statement. Ipilimumab will be supplied at a concentration of 5 mg/mL in vials containing 10 mL or 40 mL solution.

5.1.3. Storage, Handling, and Dispensing

5.1.1.1. Storage

Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored in accordance with the environmental conditions as determined by BMS and defined in the Investigator Brochure or SmPC/reference label. Ipilimumab must be stored at a temperature $\geq 2^{\circ}\text{C}$ and $\leq 8^{\circ}\text{C}$.

5.1.1.2. Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

5.1.1.3. Dispensing

It is the responsibility of the investigator to ensure that ipilimumab is only dispensed to study subjects. The ipilimumab must be dispensed only from official study sites by authorized personnel according to local regulations.

5.1.4. Drug Ordering and Accountability

5.1.1.4. Initial Orders

Following submission and approval of the required regulatory documents, a supply of ipilimumab may be ordered from BMS. Investigators must complete a Drug Request Form and email it to: distribution.allentown@thermofisher.com. If for any reason the e-mail drug request form is not successfully transmitted, contact Emily Kahora at Fisher Clinical Services T: +1 484.538.2121 F: +1 610.871.9382 E: emily.kahora@thermofisher.com or www.fisherclinicalservices.com.

It is recommended you send a test message to the Fisher Clinical Service e-mail address upon receipt of the Drug Request Form. Please include in the subject line: BMS IST Drug Order -Test .

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

This will ensure your site is recognized by Fisher and your future orders will be received without incident.

Ipilimumab vials (40 mL) are shipped in quantities of five. The initial order should be limited to 25 vials (5 cartons of 5 vials each). Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from Fisher Clinical Services on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. It is imperative that only product designated for this protocol number be used for this study. To help segregate product for this study from other investigational or marketed product, stickers bearing the BMS protocol number will be provided and should be affixed to the front of the outer carton just above the company names so as not to obscure any marking.

5.1.1.5. Re-Supply

Reorders should be emailed directly to Fisher Clinical Services (distribution.allentown@thermofisher.com) for shipment within 5 business days. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 5 business days from BMS receipt of request. Drug is not patient specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

5.1.5. Ipilimumab Accountability

It is the responsibility of the investigator to ensure that a current record of ipilimumab disposition is maintained at each study site where ipilimumab is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.
- Dates and initials of person responsible for each ipilimumab inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount destroyed at study site.

5.1.6. Ipilimumab Destruction

If ipilimumab is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.



6.0 CRITERIA FOR SUBJECT ELIGIBILITY

For entry into the study, the following criteria MUST be met. Any exceptions from the protocol-specific selection criteria must be approved by the Principal Investigator and/or the Institutional Review Board (IRB) before enrollment.

6.1 Subject Inclusion Criteria

- 1) Willing and able to give written informed consent.
- 2) Histologic diagnosis of melanoma with in transit metastasis Stage IIIB, IIIC, or IV
- 3) Required values for initial laboratory tests:
 - WBC $\geq 2000/\mu\text{L}$
 - ANC $\geq 1000/\mu\text{L}$
 - Platelets $\geq 50 \times 10^3/\mu\text{L}$
 - Hemoglobin $\geq 8 \text{ g/dL}$
 - Creatinine $\leq 3.0 \times \text{ULN}$
 - AST/ALT $\leq 2.5 \times \text{ULN}$
 - Bilirubin $\leq 3.0 \times \text{ULN}$, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)
- 4) No active or chronic infection with HIV, Hepatitis B, or Hepatitis C.
- 5) Karnofsky performance status ≥ 60
- 6) Men and women, ≥ 18 years of age.

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not post-menopausal. Post-menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause, or
- For women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level $\geq 35 \text{ mIU/mL}$.

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of ipilimumab.

6.2 Subject Exclusion Criteria

- 1) Any other malignancy that requires active treatment.
- 2) Autoimmune disease: Patients with a history of inflammatory bowel disease are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome).
- 3) Any underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of ipilimumab hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.
- 4) Patients with underlying heart conditions who are deemed ineligible for surgery by cardiology consult
- 5) Any history of prior treatment with ipilimumab or prior CD137 agonist or CTLA-4 inhibitor or agonist.
- 6) Concomitant therapy with any of the following: IL-2, interferon, or other non-study immunotherapy regimens; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids.
- 7) Women of childbearing potential (WOCBP), defined above in Section 4.1, who:
 - a. are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for at least 8 weeks after cessation of study drug, or
 - b. have a positive pregnancy test at baseline, or
 - c. are pregnant or breastfeeding.
- 8) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious) illness.
- 9) Persons of reproductive potential must agree to use an adequate method of contraception throughout treatment and for at least 8 weeks after ipilimumab is stopped.

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. All WOCBP MUST have a negative pregnancy test before first receiving ipilimumab. If the pregnancy test is positive, the patient must not receive ipilimumab and must not be enrolled in the study.



6.3. Prohibited and Restricted Therapies During the Study

6.3.1. Prohibited Therapies

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease unless indicated as a component of the protocol regimen (including those for common medical conditions) for up to one month pre and post dosing with ipilimumab.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other (non-CA184024 related) CTLA-4 inhibitors or agonists
- CD137 agonists
- Immunosuppressive agents
- Chronic systemic corticosteroids
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).

6.3.2. Restricted Therapies

Not applicable

6.3.3. Precautions

Caution is advised when considering treatment with high-dose IL-2 in patients who have previously been administered ipilimumab, particularly in patients who experienced ipilimumab-related diarrhea/colitis. Colonoscopy or sigmoidoscopy with biopsy may be advisable prior to IL-2 administration once the patient is no longer receiving ipilimumab.

7.0 RECRUITMENT PLAN

This is a single-institution phase II trial with a primary outcome of progression free survival. Patients with advanced Stage IIIB, Stage IIIC, or Stage IV melanoma with in transit disease requiring ILI will be candidates for the trial. These patients will be identified by the research assistant and/or attending physician and offered participation.

Protocol investigators treating patients at both MSKCC Manhattan and West Harrison sites will screen their patient's medical records to identify potential research subjects. Protocol treatment and procedures, however, can only take place at the Manhattan sites. Potential research subjects identified at the West Harrison site will be offered study participation and treatment at the Manhattan sites. Only consent can be obtained at the West Harrison site.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.0 PRETREATMENT EVALUATION

Prior to ILI, patients will undergo an extent of disease evaluation consisting of a CT scan or MRI of the brain, and a CT scan of the chest, abdomen and pelvis (a body PET/CT scan will suffice). The lesions will be measured and photographed. In the case of diffuse, numerous extremity lesions, three index lesions will be chosen to measure and characterize. In patients with deep lesions which are difficult to quantitate, a CT Scan of the extremity will also be performed. The patient will then undergo an ILI in the operating room under anesthesia as previously described and currently performed here at MSKCC[28]. Prior to receiving the first dose of Ipilimumab, patients will also have TSH drawn.

9.0 TREATMENT/INTERVENTION PLAN

Briefly, ILI consists of placement of angiographic catheters in the interventional radiology suite from the contralateral vessels into the femoral or axillary vessels of the affected extremity. The patient is placed on systemic heparin at the time of the catheter placement and then transported to the operating room. As prophylaxis against nausea, a single dose of a 5-HT₃ receptor antagonist, such as palonosetron 250mcg IV and dexamethasone or methylprednisolone 20mg IV is given. A pneumatic tourniquet is placed at the appropriate level around the extremity to exclude it from the

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

systemic circulation. A hot air blanket is wrapped around the extremity and the OR room is warmed, temperature probes are placed in the skin, and once the extremity reaches a temperature of 37, the procedure begins. Papaverine, 60 mg over 1 to 3 minutes is delivered through the extremity and the tourniquet is inflated. Melphalan and dactinomycin are added to 400ml of heparinized normal saline for the lower extremity and 200ml of heparinized normal saline for the upper extremity. The dose of melphalan used is 5-10 mg/L limb volume (maximum 100 mg). The dose of Dactinomycin to be used is 50-100 mcg/L limb volume (maximum 500 mcg). The drugs are infused via a pressurized circuit into the isolated limb via the arterial catheter. The infusate is then circulated using a large syringe and a wide-bore, high-flow, three-way stopcock. Blood is repeatedly withdrawn from the venous catheter and re-injected into the arterial catheter manually using the stopcock. The tubing passes through a blood warming coil maintained at 41°C. After 30 minutes, the limb is flushed with 500 cc to 1000 cc of crystalloid solution at room temperature and discarded using the 3-way stopcock and syringe. When the effluent is cleared and 60 to 80% of the flush volume has been extracted, the arterial and venous catheters are removed and protamine is administered to reverse the heparin. A percutaneous closure device may be used in selected patients (Perclose, Inc, Menlo Park, CA) by the interventional radiologist, or, firm pressure will be held for 20-30 minutes.

Blood samples will be taken for research from each patient at the following time points: at ILI (pre-treatment), during induction phase of Ipilimumab (week 1-3, week 4-6, week 7-9, week 10-12, week 13-15, and with each dose of Ipilimumab during the maintenance phase. If a patient is no longer receiving Ipilimumab while still on study, the patient will not have research bloods drawn. Tissue samples of the tumor will be taken from each patient at the following time point throughout the study: during ILI, week 1-3, and week 13-15. If the lesions are decreasing in size prior to week 13-15, a biopsy may be performed prior to the week 13-15 time point. As noted, a patient may refuse any biopsy and stay on study, and no biopsy will be performed at the week 13-15 evaluation if there is no identifiable lesion or pigmented scar. In the latter case, photographs of the lesion site will still be taken. An additional biopsy may be performed during the induction phase (prior to week 13-15), if the physician feels the patient is responding and the lesion is likely to be gone by week 13-15.

After recovery from ILI patients will be seen in the office to assess recovery, and to start systemic immunotherapy. Ipilimumab will begin 1-3 weeks, or until resolution of Weiderbink Toxicity (appendix 7) to grade I-III after the ILI procedure. If a patient has severe toxicity after ILI (grade IV or V), they will not receive Ipilimumab therapy.

Again, the lesions will be photographed and measured and blood sampled for research purposes. Patients will then receive Ipilimumab every 3 weeks for a total of 4 total doses. Blood will be taken at each dose of Ipilimumab. Three weeks (+/- a week) following the final dose of Ipilimumab the lesion site will be biopsied, if there is an identifiable lesion or pigmented scar, and blood samples will again be taken for analysis. The lesion site will also be photographed. Patients will be allowed to skip a dose of Ipilimumab, after the first dose, if the performance status is not adequate, but the dosing cannot be delayed (see Appendix 8 for study schema). Patients completing this induction phase will then be entered into the maintenance stage of the study, with dosing of Ipilimumab dosing every 3 months (+/- 2 weeks). After completing the induction phase, a CT scan will be completed with a finalized report before ordering and infusing the maintenance dose of Ipilimumab. Patients



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

who have discontinued the study drug and have not progressed will be seen at all specified time points for the intended duration of the trial (+/- 4 weeks).

The Wiederbink criteria will be used to assess toxicity, as shown in Appendix 7. A partial and complete response will be assessed as previously described.²⁷

Biopsies will be performed with in the OR or the clinic with a punch biopsy needle. If not already under general anesthesia, this will require infiltration of local anesthesia, a punch biopsy and a suture to close the lesion. One portion of the tissue will be snap frozen, and another will be kept sterile for immediate analysis of T cell infiltrate. Slides will be made for analysis of presence of melanoma and additional stains will be performed to characterize the immune infiltrate, as described below. All biopsies and blood samples will be processed at the Ludwig Center for Cancer Immunology at MSKCC, Dr. Wolchok is the associate director of this laboratory which is in Zuckerman.

Phenotypic staining: The Ludwig Center has developed several panels of phenotypic markers to assess T cell before and after therapy. These include activated/memory cells and regulatory T cells. A typical experiment can be summarized as follows: One million PBMCs, or Tumor infiltrating lymphocytes are stained with the antibodies in Table above. Acquisition is done on a CYAN flow cytometer with Summit software (DakoCytomation California Inc., Carpinteria, CA). Analysis is performed using FlowJo software (version 8.1; TreeStar, Inc., Ashland, OR).

Antibody	Fluorochrome	Source
Anti-hu-CD3	Pacific Blue	eBioscience
Anti-hu-CD4	ECD	Beckman Coulter
Anti-hu-CD8	PE	BD Bioscience
Anti-hu-PD-1	FITC	BD Bioscience
Anti-hu-CD25	APC-Cy7	BD Bioscience
Anti-hu-FOXP3	APC	eBioscience
Anti-hu-ICOS	PE-Cy7	eBioscience
Anti-hu-IgG1a	PE-Cy7	Dako
Anti-hu-IgG2a	APC	Dako

T-cell stimulation ex vivo and intracellular cytokine staining: In order to study the impact of IL1/Ipilimumab on T cell function, we have standardized an ex vivo T cell assay to assess the T cell response to CEF peptide pools (AnaSpec Inc. Fremont, CA) or Staphylococcus Enterotoxin B (SEB, Sigma-Aldrich, St. Louis, MO). The CEF peptide pools contain a group of 32 peptides that cover HLA class I restricted T cell epitopes of Cytomegalovirus, Epstein-Barr Virus, and Flu Virus (CEF). CEF peptide pools are used to activate viral antigen specific CD8+ T cells. Freshly thawed lymphocytes are stimulated with CEF (1 mg/ml) or staphylococcal enterotoxin B (SEB, 1 mg/ml). The cells are stained for CD3, CD8 and CD4 and then fixed and permeabilized before staining with FITC-IFN-g. Samples are acquired on a CYAN flow cytometer and analyzed as above. Gating for each cytokine is based on a positive control sample stimulated with SEB and on an unstimulated sample.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

Antibody responses: Antibody responses to the tumor antigens TYRP-1, TYRP-2, tyrosinase, Melan A, and NY-ESO-1 will be measured using a standard ELISA with recombinant antigens produced in *E. coli* as previously described. Positive results in the ELISA will be defined as extrapolated reciprocal titers > 100.

T-cell responses: Intracellular cytokine staining using pools of overlapping peptides covering antigens which are frequently recognized by T cells in melanoma patients will be employed to assay CD4+ and CD8+ T cell responses. The antigens which we will focus on include: TYRP-1, TYRP-2, tyrosinase, Melan A, gp100 and NY-ESO-1. Pentadecapeptides overlapping by 10 amino acids will be synthesized for the above antigens and any other targets which are found in the serologic screening. Flow cytometry will be performed as above. We define a positive response if at any post-vaccination time point there was an increase of ≥ 3 SDs from baseline and a frequency of IFN γ + CD4+ or CD8+ > 0.1% after 10-day in vitro stimulation.

In situ immune monitoring: For each tumor biopsy we will analyze the immune infiltrate. We have experience with this and have been able to identify the phenotype of infiltrating cells using flow cytometry and have even been able to monitor tetramer+ and/or tumor antigen specific IFN- γ + T cells *in situ* by flow cytometry. In situ tumor monitoring focuses on three major methodologies: the phenotypic characterization of tumor-infiltrating lymphocytes (TILs) with multiparametric flow cytometry, the characterization of antigen-specific T cell responses and immunohistochemical (IHC) characterization of tumor and peri-tumoral tissue. Phenotypic characterization of TILs includes the quantitation of CD25 and FOXP3 expression, as well as inducible costimulator (ICOS) expression. The phenotype of TILs are compared to that of PBMCs to determine if there are illustrative differences.

Treatment/Location:

ILI with Melphalan and Dactinomycin- MSKCC operating room.

Ipilimumab- IV administration in outpatient chemotherapy clinic

9.1. Ipilimumab

Each patient will receive ipilimumab 10mg/kg every 3 weeks for a total of four doses. Infusions will be given over 90 minutes, not by bolus or IV push.

Ipilimumab (BMS-734016) is a human immunoglobulin G (IgG1) κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without nonspecific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates, including cynomolgus monkeys.

9.1.1. Dose Calculations

Calculate Total Dose as follows:

$$\text{Patient body weight in kg} \times [10 \text{ mg}] = \text{total dose in mg}$$

Calculate Total Infusion Volume as follows:

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

Total dose in mg \div 5 mg/mL = infusion volume in mL

Calculate Rate of Infusion as follows:

Infusion volume in mL \div 90 minutes = rate of infusion in mL/min.

For example, a patient weighing 114 kg (250 lb) would be administered 1140 mg of ipilimumab (114 kg \times 10 mg/kg = 1140 mg) with an infusion volume of 228 mL (1140 mg \div 5 mg/mL = 228 mL) at a rate of approximately 2.5 mL/min (228 mL \div 90 minutes) in 90 minutes.

9.1.2. Storage, Preparation, and Administration

Ipilimumab Injection, 50 mg/vial (5 mg/mL) or 200 mg/vial (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of Ipilimumab Injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to concentrations between 1 mg/mL and 4 mg/mL and stored in PVC, non-PVC or glass containers for up to 24 hours at 2-8°C or RT/RL.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

9.1.3. Preparation and Administration Guidelines

The supplies needed for ipilimumab preparation and administration include calibrated syringes and infusion containers. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with a 0.2 μ m or 1.2 μ m in-line polyethersulfone or 1.2 μ m positively charged nylon filter to complete the infusion in 90 minutes, with a 10-mL normal saline flush at the completion of the infusion.

- 1) As ipilimumab is stored at refrigerated temperatures (2-8°C), allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.
- 2) Aseptically withdraw the required volume of ipilimumab solution into a syringe. Insert the needle at an angle into the ipilimumab vial by placing the needle – bevel side down – against the glass, with the tip touching the neck of the vial. The initial solution concentration is 5 mg/mL. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].
- 3) Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
- 4) Inject ipilimumab solution withdrawn into an appropriate size evacuated infusion bag to produce a final infusion volume that has been calculated from the weight of the patient. For example, if preparing a 10mg/kg treatment for a 65 kg patient you will use 13 vials (or 650 mg), the drug solution volume will be 10 mL per vial or 130 mL total.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

- 5) If the total dose calculates to less than 90 mL of solution then the total dose needed should be diluted to a total volume of 90 mL in 0.9% sodium chloride.
- 6) Mix by GENTLY inverting several times. DO NOT shake.
- 7) Visually inspect the final solution. If the initial diluted solution or final dilution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
- 8) Do not draw into each vial more than once. Any partial vials should be safely discarded and should not be stored for reuse.

Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents. Ipilimumab is administered as an IV infusion only.

In accordance with the FDA approved label, patients participating will have their TSH level drawn at baseline and before each dose. However, the TSH level does not have to be known at the time of dosing with Ipilimumab as treatment modifications should be based on signs and symptoms related to endocrinopathies consistent with existing guidelines within the investigator brochure and protocol. If a subject has thyroid dysfunction and concomitant symptoms (i.e. fatigue), the subject should be monitored more frequently and be treated as per standard medical practice. Appendix 6 references the Endocrinopathy Management Algorithm. Dose modifications for study medication should follow protocol guidelines.

9.1.4. Dose Modifications

Patients may develop study drug-related toxicities that may require skipping doses or dose discontinuation. Some of these adverse events may be consistent with potentially drug-related immune-mediated phenomena; termed IRAEs (Appendix 2, Appendix 3). Details of how to dose study medication in the present of adverse drug reactions that may or may not be IRAEs are addressed below.

Treatment modifications will be made based on specified safety criteria. Patients will delay or discontinue treatment with ipilimumab if they experience at least one adverse event, specified below, considered by the investigator to be certainly, probably, or possibly related to ipilimumab treatment. Additionally, refer to appendix 3 and 4 for treatment and dose modification clarification. The following criteria will be used to determine dosing delay, restarting doses, or discontinuing ipilimumab.

Delay ipilimumab dosing for the following related adverse events:

It may be necessary to skip study drug dosing for the following related adverse event(s):

- Any \geq Grade 2 non-skin related adverse event (including IBEs), except for laboratory abnormalities
- Any \geq Grade 3 laboratory abnormality

It is necessary to skip study drug dosing for the following adverse events:

- Any \geq Grade 3 skin-related adverse event regardless of causality.

Restart ipilimumab dosing if/when the adverse event(s) resolve(s) to \leq Grade 1 severity or returns to baseline within 3 weeks of initial dose administration:

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

- If the adverse event has resolved, restart ipilimumab dosing at the next scheduled time point per protocol.
- If the adverse event has not resolved in the protocol-specified dosing window (3 weeks \pm 3 days), the next scheduled dose will be omitted.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 2: Time and Events Schedule for Protocol 10-101

	Pre-study	ILI	Wk 1	Wk 1-3	Wk 4-6	Wk 7-9	Wk 10-12	Wk 13-15 (+/- 1 week)	3 Months (+/- 2 weeks) ¹
Consent	X								
PE	X		X	X	X	X	X	X	X
Tumor Assess	X							X	X
Normal Labs (CBC, Comp)			X	X	X	X	X	X	X
Pre-study Labs (CBC, Comp, HIV/ Hep B/ Hep C)	X								
EKG	X								
PBMC/Serum		X		X	X	X	X	X	X
Biopsy		X		X				X	
ILI		X							
Ipilimumab				X	X	X	X		X
KPS	X							X	
Photograph	X							X	
Body PET/CT or CT C/A/P	X								
CT C/A/P								X	X
Finalized Report								X	
CT/MRI Brain	X								
Limb Toxicity Form	X			X		X		X	
Ipilimumab Tox Assessment				X	X	X	X		X
Lesion Measurement Form	X							X	X

10.1. Procedures by Visit

The Time and Events Schedule summarizes the frequency and timing of various measurements.

10.2. Study Completion or Early Discontinuation Visit

At the time of study early withdrawal, the reason for early withdrawal and any new or continuing adverse events should be documented.

¹ +/- 4 weeks for patients off treatment



10.3. Study Drug Discontinuation

If study drug administration is discontinued, the reason for discontinuation will be recorded.

10.4. Study Materials

Bristol-Myers Squibb (BMS) will provide ipilimumab at no cost for this study.

11.0 TOXICITIES/SIDE EFFECTS

11.1. Safety Assessments

All patients who receive at least one dose of ipilimumab will be considered evaluable for safety parameters. Additionally, any occurrence of a SAE from time of consent forward, up to and including follow-up visits will be reported. See Section 17.2: Serious Adverse Event (SAE) Reporting.

Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (<http://ctep.cancer.gov>). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

11.2. Safety Evaluation

11.2.1. Safety with Ipilimumab

Prior trials with Ipilimumab have demonstrated that the medicine can cause mild symptoms with infusion such as diaphoresis, or headaches. Patients may also develop low-grade constitutional symptoms such as fatigue, nausea, arthralgias, myalgias and fevers. Females and males should be aware of the potential reproductive side effects while participating in this study.

The high-grade toxicities associated with Ipilimumab are severe autoimmune reactions or immune breakthrough events (IBE). For the purposes of this study, IBE is defined as any event immune event that is associated with drug exposure. These side effects have been well described and include diarrhea/colitis, hypophysitis, hepatitis, uvetitis, nephritis, vitiligo and rash. Depending on the trial, the risk of Grade 3-4 immune-related adverse events is 12 to 41% as discussed above.

Diarrhea/colitis is one of the most serious and must be evaluated in a timely fashion (see diarrhea algorithm in Appendix 4). All patients with diarrhea will be seen by physician and evaluated with a CT Scan/colonoscopy if necessary. The standard criteria for stopping Ipilimumab will be used. This includes any grade 4 lab abnormality or any grade 3 lab abnormality related to Ipilimumab (except elevated AST/ALT, where values >8x upper limits of normal will be used). Any evidence of Grade 3 diarrhea/colitis, ongoing symptomatic endocrinopathies will similarly be dose limiting.

The following criteria will be used to determine if/when to skip, restart, or discontinue study drug dosing.

Skip drug dosing for the following related adverse events:

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

- Any Grade 2 non-skin related adverse event (including IBE's)
- Any Grade 3 skin-related adverse event (including IBE's)

When the adverse event(s) resolve to \leq Grade 1 severity

- If the adverse event has resolved, restart dosing at the next scheduled time point per protocol
- If the adverse event has not resolved in the protocol-specified dosing window, the next scheduled dose will be skipped and dosing will be resumed at the subsequent scheduled dose.
- If > 1 dose is expected to be skipped, the dosing schedule modifications must be discussed with the clinical research organization (CRO) medical monitor prior to implementation.

Permanent discontinuation of study drug for related adverse events or other criteria.

Any \geq Grade 3 eye pain or reduction of visual acuity or any \leq Grade 2 ocular toxicity that does not respond to topical therapy.

- Any \geq Grade 3 bronchospasm or other hypersensitivity or other hypersensitivity reaction
- Any other \geq Grade 3 non-skin related adverse event with the exception of the events listed under "Exceptions to Permanent Discontinuation" (below)
- Any \geq Grade 4 adverse event
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with the continued study drug dosing.

Exceptions to Permanent Discontinuation

In selected situations, temporary discontinuation will occur until toxicity resolves to \leq Grade 1 severity. Re-starting of doses will be based on the criteria defined above. Such exceptions are:

- Potentially reversible inflammation ($<$ Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis;
- Hospitalization for \leq Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up
- Patients with the following conditions where the investigator's opinion continuing study drug administration is justified:
- Any \leq Grade 2 ocular toxicity that has responded to topical therapy
- Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy.

Note: Study drug may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

11.2.2. Safety related to ILI



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

Melphalan has been used for regional chemotherapy for metastatic melanoma since 1957. It has proven efficacy and safety in conjunction with Dactinomycin in the use of ILI. The most common side effects of both of these drugs is myelosuppression, however, none of the patients had myelosuppression in the ILI trial performed at MSKCC. Dactinomycin, a chemotherapy that will be used in ILI has also caused Myelosuppression.

ILI has been shown to be effective and safe. The most common toxicity from limb perfusion is soft tissue damage. This includes erythema of the skin, blistering and sloughing of the epidermis, nail loss, edema of the soft tissues, limb pain, and pain at site of biopsy. A well established system to score acute limb toxicity (Weiderbink Toxicity Scale, Appendix 7) will be used to grade limb toxicity.

All patients experiencing Grade 4 or 5 limb toxicity will be removed from treatment. We will keep them on the study, and continue to follow them within the intention to treat analysis, but they will not receive any more therapy with Ipilimumab. If a Grade 4 or 5 toxicity occurs again, the study will be terminated.

If Grade 3 limb toxicity occurs, the Ipilimumab will be held until it returns to Grade 0-1. Patients receiving Ipilimumab must be monitored carefully for the development of immune breakthrough events, as blocking CTLA-4 may allow the emergence of auto-reactive T cells as discussed above.

11.3. Immune-Related Adverse Events (IRAEs): Definition, Monitoring, and Treatment

Blocking CTLA-4 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive autoimmune events, now termed IRAEs, noted in previous ipilimumab studies.

For the purposes of this study, an IRAE is defined as an AE of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an IRAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected IRAEs must be documented on an AE or SAE form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic IRAE (e.g., systemic lupus erythematosus-like diseases) or organ-specific IRAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an IRAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary. See Appendix 3 for suggested work-up and treatment of IRAEs.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as \geq Grade 3 diarrhea requires corticosteroid treatment. See Appendix 4 for additional details.



11.3.1. Treatment of Infusion Reactions Associated with Ipilimumab

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.

- For mild symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash):
 - Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
 - Complete the ipilimumab infusion at the initial planned rate.
 - Diphenhydramine 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.
 - Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of ipilimumab.
- For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):
 - Interrupt ipilimumab.
 - Administer diphenhydramine 50 mg IV.
 - Monitor patient closely until resolution of symptoms.
 - Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
 - Resume ipilimumab infusion after recovery of symptoms.
 - At the discretion of the treating physician, ipilimumab infusion may be resumed at one half the initial infusion rate, then increased incrementally to the initial infusion rate.
 - If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
 - The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.
 - At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.
- For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mm Hg, or angioedema):
 - Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.
 - Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with solumedrol 100 mg IV, as needed.
 - Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
 - No further ipilimumab will be administered.



- In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

11.3.2. Treatment of Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1. Efficacy Evaluation

The physician will identify assessable extremity lesions pre-infusion which will be measured and recorded on the pre-infusion data sheet. This will involve marking the selected sites on an anatomic diagram of the extremity and supplying the measurements of these sites, using the diagram supplied in appendix 10. In patients with extensive, small deposits of tumor, a description of the size of 3 index lesions and approximate number will suffice for pre-infusion documentation. Pre-infusion photographs will be taken with a ruler along lesions.

Tumor assessment will be measured by the immune related response criteria (irRC), as discussed below. Progression free survival, from time of ILI, will be determined by measuring the index lesions, non-index lesions, and new lesions as described below. Patients with deep lesions will have repeat CT Scan evaluation to quantitate the lesions. Since many patients have been noted to have lesions which initially progress on therapy with Ipilimumab, progression free survival rate will be determined at 12 months.

12.2. Definition of Measurable/Non-Measurable and Index/Non-Index Lesions

Definitions of lesions are based on modified immune related response criteria, irRC, developed by Dr. Wolchok and described below[32].

12.3. Definition of Measurable and Non-Measurable Lesions

- Measurable Lesions are lesions that can be accurately measured in two perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular. Skin lesions can be considered measurable, and are the primary lesions being measured in this study.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

- Non-Measurable (evaluable) Lesions are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following:
 - Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.
 - All measurable and non-measurable lesions should be measured at screening and at the defined tumor assessment time points (section 6, table). Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

12.4. Definition of Index/Non-Index Lesions

All measurable lesions, up to a maximum of three lesions per extremity and ten lesions in total, should be identified as index lesions to be measured and recorded on the medical record at Screening. In addition, index lesions should be selected based on their size (lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the patient's tumor burden. At Screening, a sum of the products of diameters (SPD) for all index lesions will be calculated and considered the baseline sum of the products of diameters. Response criteria to be followed are listed below. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at tumor assessment (TA).

Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be recorded on the medical record and should be evaluated at the same assessment time points as the index lesions. In subsequent assessments, non-index lesions will be recorded as "stable or decreased disease," "absent," or "progression."

12.5. Definition of Tumor Response Using irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear[32].

12.6. Definition of Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR): Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index and all new measurable lesions (ie., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by $\geq 25\%$ when compared to SPD at nadir.
- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of progressive disease.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

- irProgressive Disease (irPD): At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all index lesions and any new lesions) when compared to SPD at nadir.

12.7. Definition of Non-Index Lesions Response Using irRC

- irComplete Response (irCR): Complete disappearance of all non-index lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- irPartial Response (irPR) or irStable Disease (irSD): non-index lesion(s) are not considered in the definition of PR, these terms do not apply.
- irProgressive Disease (irPD): Increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

12.8. Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

12.9. Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- Immune-Related Complete Response (irCR): Complete disappearance of all tumor lesions (index and nonindex together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- Immune-Related Partial Response (irPR): The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- Immune-Related Stable Disease (irSD): irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- Immune-Related Progressive Disease (irPD): It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
 - At least 25% increase in the sum of the products of all index lesions over baseline SPD calculated for the index lesions.
 - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.



Table 3: Immune-Related Response Criteria Definitions

Index Lesion Definition	Non-Index Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	$\geq -50\%$	irPR
				$<-50\%$ to $<+25\%$	irSD
				$>+25\%$	irPD
Stable Disease	Any	Any	Any	$<-50\%$ to $<+25\%$	irSD
				$>+25\%$	irPD
Progressive Disease	Any	Any	Any	$\geq +25\%$	irPD

12.10. Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

12.11. Response Endpoints

Ipilimumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters (based on study indication, ie, hematologic malignancies) within 12 weeks following start of ipilimumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

Therefore, patients with tumor volume increase detected or lack of laboratory parameter response documentation prior to week 12 but without rapid clinical deterioration should continue to be treated with ipilimumab and clinically observed with a stringent imaging schedule to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of ipilimumab and more likely capture its true potential to induce clinical responses.

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1. Discontinuation of Study Therapy

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Pregnancy
 - All WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on study pregnancy tests for WOCBP enrolled in the study.
 - The investigator must immediately notify BMS in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by Bristol-Myers Squibb (BMS).
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

13.2. Permanent Discontinuation for Related Adverse Events

- Any \geq Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to \leq Grade 1 severity within 2 weeks of starting therapy, OR, requires systemic treatment.
- Any \geq Grade 3 bronchospasm or other hypersensitivity reaction.
- Any other \geq Grade 3 non-skin related adverse event with the exception of events listed under "No Discontinuation" (below).
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.



13.3. Exceptions to Permanent Discontinuation

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Hospitalization for \leq Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:
 - Ocular toxicity that has responded to topical therapy.
 - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. Note: Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

14.0 BIOSTATISTICS

This is a phase II study of the addition of ipilimumab to isolated limb infusion with standard melphalan and dactinomycin. The primary objective of the study is to safety and efficacy in this patient population with the primary efficacy measure defined as progression-free survival (starting from the date of ILI) at 1 year (week 48-54). Due to the length of time required to observe the primary endpoint, efficacy evaluation will be based on a single stage design with an alpha level of 0.1. Based upon the only prospective trial of patients with ILI, performed at MSKCC, the 23% of patients had a complete response with a median duration of one year[29]. This trial estimates a progression-free survival in patients with advanced stage melanoma of approximately 30%; with the proposed treatment regimen it is hypothesized that one year progression-free survival will improve to 50%. Thirty-nine patients will be accrued. If 16 or more out of 39 are progression-free at one year the regimen would have demonstrated acceptable effectiveness. With 39 patients the study will have 90% power with level of significance of 10%.

Response rate will be assessed according to the immune related response criteria outlined in section 6.4.3. Proportion of responding patients along with 95% confidence interval will be reported. Patients will be followed for toxicity. Acute limb toxicity will be assessed using the Weiderbink Toxicity scale (Appendix 7). If at any point in the study a grade 4 or 5 Wiederbink toxicity is observed in any patients, the dose of ipilimumab will be reduced to 3mg/kg. If grade 4 or 5 toxicity occurs again in a separate patient, the study will be terminated. All other toxicities will be tabulated according NCI Common Toxicity Criteria.

Summaries of antibody response, comparison of pretreatment with post-ipilimumab and end of treatment will be assessed for percent of CD4 and CD8 cells as well as CD25, FOXP3, ICOS, CD45, CD67 and CD152 cells among others. This will be exploratory and results will be descriptive.

It is anticipated that 2 patients per month will be accrued to the study and the study will be completed in approximately 2-3 years.



15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (<http://ppr/>). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

This study does not involve randomization.

16.0 DATA MANAGEMENT ISSUES

All data will be collected by an RSA. A CRDB database will be created on a password locked server at MSKCC for access to the data limited to the study coordinators. It is estimated that this study will accrue approximately 39 patients over a 3 year period.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1. Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in the final approved protocol. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to your BMS protocol manager.

All revisions (protocol amendments, administrative letters, and changes to the informed consent) must be submitted to your BMS protocol manager. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

See also 21CFR for definitions of amendment and requirements.

16.1.2. Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

Study treatment and procedures, outlined in the Treatment/Intervention Plan above, will only take place at MSK Manhattan sites. Potential research subjects identified at the MSK West Harrison site will be offered study participation after being informed that all study treatment and procedures must take place at the Manhattan sites. Investigators and their research team, following the informed consent process described above, may obtain written informed consent from subjects at the MSK West Harrison site. Only consent, however, can be obtained at the West Harrison site.

16.1.3. Records and Reports

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation (e.g. medical record) on each individual treated with Ipilimumab or entered as a control in the investigation. The investigator is required to retain, in a confidential manner, the data pertinent to the study.

16.1.4. Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

Systems with procedures that ensure the quality of every aspect of the study will be implemented.

16.1.5. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures

16.1.6. Records Retention

The investigator must retain Ipilimumab disposition records, source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. medical record) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Documentation of such transfer must be provided to BMS.

Individuals treated with Ipilimumab or entered as a control in the investigation. The investigator is required to retain, in a confidential manner, the data pertinent to the study.

Data will be captured in Clinical Research Database (CRDB) along with the clinical data capture tools in Appendix 7.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:

<http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://mskweb2.mskcc.org/irb/index.htm>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

Informed consent will be obtained from all research subjects. The informed consent document will explain to the subjects the risks, benefits, toxicities/side effects, alternatives/options for treatment, and financial costs/burdens. Participation in the study is voluntary. The study drug will be provided by Bristol Myers Squibb (BMS) at no cost to the patient. Patients will be billed for patient care services.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB)

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

- If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 Serious Adverse Event Reporting

17.2.1.1. Collection of Safety Information

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

17.2.1.2. Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see "note" below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Although overdose and cancer are not always serious by regulatory definition, these events should be reported on an SAE form and sent to BMS in an expedited manner. An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important.

NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

- elective surgery, planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Note that all pregnancies, regardless of outcome, must be reported to the sponsor on a Pregnancy Surveillance Form, not an SAE form. All pregnancies must be reported and followed to outcome, including pregnancies that occur in the female partner of a male study subject. See Section 8.4 for instructions on reporting pregnancies.

17.2.1.3. Nonserious Adverse Events

All adverse events that are not classified as serious.

17.2.1.4. Assignment of Adverse Event Intensity and Relationship to Investigational Product

All adverse events, including those that are serious, will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 4.0.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used for adverse events:

- **Certain:** There is a reasonable causal relationship between the investigational product and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.
- **Probable:** There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
- **Possible:** There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.
- **Not likely:** There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- **Not Related:** There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between noninvestigational product, concurrent disease, or circumstance and the AE.

The expression “reasonable causal relationship” is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-101A(7)

17.2.1.5. Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded in the medical record.

The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

17.2.1.6. Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify BMS of any SAE occurring after this time period that is believed to be certainly, probably, or possibly related to the investigational product or protocol-specified procedure.

All SAEs whether related or unrelated to the ipilimumab, must be immediately reported to BMS (by the investigator or designee) within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site. A copy of the SAE form required by Bristol-Myers Squibb Company (BMS) is attached (appendix 9).

All SAEs should be faxed or emailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, which can be accessed at:

<http://www.accessdata.fda.gov/scripts/medwatch/>.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
<http://www.accessdata.fda.gov/scripts/medwatch/>



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-101A(7)

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page and reported expeditiously to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be immediately reported by confirmed facsimile transmission (fax) and mailing of the completed SAE page. In some instances where a facsimile machine is not available, overnight express mail may be used. If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting.

If the investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE page.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

17.2.1.7. Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (certainly, probably, or possibly related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

17.2.1.8. Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of investigational product. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

If an ongoing nonserious AE worsens in its intensity, or if its relationship to the investigational product changes, a new nonserious AE entry for the event should be completed. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with nonserious AEs at study completion should receive post-treatment follow-up as appropriate.

All identified nonserious AEs must be recorded and described in the medical record.

17.2.1.9. Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling WOCBP in this clinical study, the investigator must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test within 72 hours before receiving ipilimumab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive ipilimumab and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to BMS, and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

17.2.1.10. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.



19.0 REFERENCES

1. Lenschow, D.J., T.L. Walunas, and J.A. Bluestone, *CD28/B7 system of T cell costimulation*. Annual Review of Immunology, 1996. 14: p. 233-58.
2. Schwartz, R.H., *Costimulation of T lymphocytes: the role of CD28, CTLA-4, and B7/BB1 in interleukin-2 production and immunotherapy*. Cell, 1992. 71(7): p. 1065-8.
3. Chen, L., et al., *Costimulation of antitumor immunity by the B7 counterreceptor for the T lymphocyte molecules CD28 and CTLA-4*. Cell, 1992. 71(7): p. 1093-102.
4. Townsend, S.E. and J.P. Allison, *Tumor rejection after direct costimulation of CD8+ T cells by B7-transfected melanoma cells*. Science, 1993. 259(5093): p. 368-70.
5. Townsend, S.E., et al., *Specificity and longevity of antitumor immune responses induced by B7-transfected tumors*. Cancer Research, 1994. 54(24): p. 6477-83.
6. Allison, J.P., A.A. Hurwitz, and D.R. Leach, *Manipulation of costimulatory signals to enhance antitumor T-cell responses*. Current Opinion in Immunology, 1995. 7(5): p. 682-6.
7. Linsley, P.S., et al., *CTLA-4 is a second receptor for the B cell activation antigen B7*. Journal of Experimental Medicine, 1991. 174(3): p. 561-9.
8. Thompson, C.B. and J.P. Allison, *The emerging role of CTLA-4 as an immune attenuator*. Immunity, 1997. 7(4): p. 445-50.
9. Walunas, T.L., et al., *CTLA-4 can function as a negative regulator of T cell activation*. Immunity, 1994. 1(5): p. 405-13.
10. Kearney, E.R., et al., *Antigen-dependent clonal expansion of a trace population of antigen-specific CD4+ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4*. Journal of Immunology, 1995. 155(3): p. 1032-6.
11. Krummel, M.F. and J.P. Allison, *CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation*. Journal of Experimental Medicine, 1995. 182(2): p. 459-65.
12. Krummel, M.F., T.J. Sullivan, and J.P. Allison, *Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion in vitro and in vivo*. International Immunology, 1996. 8(4): p. 519-23.
13. Tivol, E.A., et al., *Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4*. Immunity, 1995. 3(5): p. 541-7.
14. Waterhouse, P., et al., *Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4*. Science, 1995. 270(5238): p. 985-8.
15. Chambers, C.A., T.J. Sullivan, and J.P. Allison, *Lymphoproliferation in CTLA-4-deficient mice is mediated by costimulation-dependent activation of CD4+ T cells*. Immunity, 1997. 7(6): p. 885-95.
16. Hodi, F.S., et al., *Improved survival with ipilimumab in patients with metastatic melanoma*. New England Journal of Medicine, 2010. 363(8): p. 711-23.
17. Report, C.C.S., *A Randomized, Double-Blind, Multi-center, Phase II Fixed Dose Study of Multiple Doses of Ipilimumab (MDX-010) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma*. 2008, Bristol-Myers Squibb Company and Medarex Inc.
18. Report, C.C.S., *A Multicenter, Single Arm Phase 2 Study of MDX-010 (BMS 734016) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma*. 2008, Bristol-Myers Squibb Company and Medarex Inc.
19. Report., C.C.S., *Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Comparing the Safety of Ipilimumab Administered With or Without Prophylactic Oral Budesonide (Entocort® EC) in Patients with Unresectable Stage III or IV Malignant Melanoma*. . 2008, Bristol-Myers Squibb Company and Medarex Inc.,
20. Korn, E.L., et al., *Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials*. Journal of Clinical Oncology, 2008. 26(4): p. 527-34.



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-101A(7)

21. Chapman, P.B., et al., *Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma*. Journal of Clinical Oncology, 1999. 17(9): p. 2745-51.
22. Middleton, M.R., et al., *Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma*. [Erratum appears in J Clin Oncol 2000 Jun;18(11):2351]. Journal of Clinical Oncology, 2000. 18(1): p. 158-66.
23. Bedikian, A.Y., et al., *Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group*. Journal of Clinical Oncology, 2006. 24(29): p. 4738-45.
24. Balch, C.M., et al., *An evidence-based staging system for cutaneous melanoma*. CA: a Cancer Journal for Clinicians, 2004. 54(3): p. 131-49; quiz 182-4.
25. Jaques, D.P., D.G. Coit, and M.F. Brennan, *Major amputation for advanced malignant melanoma*. Surgery, Gynecology & Obstetrics, 1989. 169(1): p. 1-6.
26. Benckhuijsen, C., et al., *Regional perfusion treatment with melphalan for melanoma in a limb: an evaluation of drug kinetics*. European Journal of Surgical Oncology, 1988. 14(2): p. 157-63.
27. Kroon, H.M., et al., *Outcomes following isolated limb infusion for melanoma. A 14-year experience*. Annals of Surgical Oncology, 2008. 15(11): p. 3003-13.
28. Brady, M.S., et al., *A phase II trial of isolated limb infusion with melphalan and dactinomycin for regional melanoma and soft tissue sarcoma of the extremity*. Annals of Surgical Oncology, 2006. 13(8): p. 1123-9.
29. Noorda, E.M., et al., *Isolated limb perfusion: what is the evidence for its use?* Annals of Surgical Oncology, 2004. 11(9): p. 837-45.
30. Kroon, H.M., et al., *Isolated limb infusion as palliative treatment for advanced limb disease in patients with AJCC stage IV melanoma*. Annals of Surgical Oncology, 2009. 16(5): p. 1193-201.
31. Hersh, E., et al., *Long-term survival of patients (pts) with advanced melanoma treated with ipilimumab with or without dacarbazine*. J Clin Oncol (Meeting Abstracts), 2009. 27(15S): p. 9038-.
32. Wolchok, J.D., et al., *Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria*. Clinical Cancer Research, 2009. 15(23): p. 7412-20.

20.0 APPENDICES

APPENDIX 1	LIST OF ABBREVIATIONS
APPENDIX 2	GENERAL RECOMMENDATIONS FOR IMMUNE-RELATED ADVERSE EVENTS (IRAES)
APPENDIX 3	SUGGESTED WORK-UP AND TREATMENT FOR IMMUNE-RELATED ADVERSE EVENTS (IRAES)
APPENDIX 4	DIARRHEA MANAGEMENT ALGORITHM
APPENDIX 5	HEPATOTOXICITY MANAGEMENT ALGORITHM
APPENDIX 6	ENDOCRINOPATHY MANAGEMENT ALGORITHM
APPENDIX 7	WIEDERBINK CRITERIA
APPENDIX 8	SCHEMA STUDY

Amended: 09/16/15



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL

IRB#: 10-101A(7)

APPENDIX 9	SAE FORM
APPENDIX 10	EXTREMITY TUMOR ASSESSMENT FORMS
APPENDIX 11	VIDEO FOR PATIENTS AVAILABLE ON MSKCC.ORG (EXTERNAL)
APPENDIX 12	SKIN TOXICITY MANAGEMENT ALGORITHM
APPENDIX 13	NEUROLOGICAL TOXICITY MANAGEMENT ALGORITHM
APPENDIX 14	10-101 PATIENT STUDY CALENDAR